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Synthesis of *cis*-3-hydroxypipecolic acid via SmI_2-mediated cyclization of aldehydo β-aminovinyl sulfoxides

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ABSTRACT

Stereoselective synthesis of *cis*-3-hydroxypipecolic acid was achieved via chirality transfer in the SmI_2-mediated cyclization reactions of aldehydo β-aminovinyl sulfoxides.

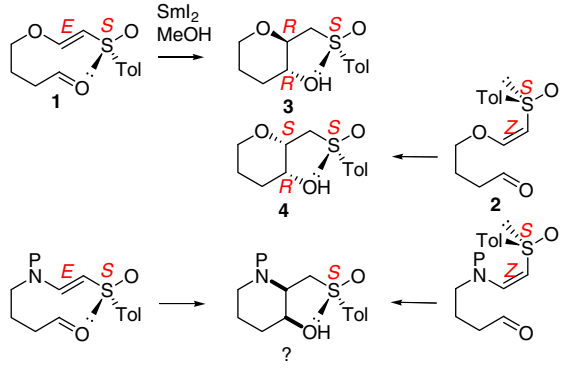
Recently, SmI_2-mediated cyclization of aldehydo β-alkoxyvinyl sulfoxides emerged as a viable method for construction of 3-hydroxyoxolanes and 3-hydroxyoxanes.[1,2] Cyclizations of aldehydo β-alkoxyvinyl sulfoxides derived from primary and tertiary alcohols appear to proceed under sulfoxide chirality control, and the stereochemistry of the major products may be predicted on the basis of the olefin geometry and sulfoxide chirality. For example, the reaction of β-alkoxyvinyl sulfoxide **1** with SmI_2 in the presence of methanol proceeded smoothly to yield a single 3-hydroxyoxane product **3**. Reaction of the (*Z*)-(*S*)-isomer **2** also produced a single cyclization product **4** (Scheme 1). We were curious whether the same kind of stereoselectivity and stereospecificity may be maintained in the cyclization of aldehydo β-aminovinyl sulfoxides, and wish to report here the results of our recent studies in this area of research.

At the outset, we settled on the Ses-protection of the amino group considering the efficiency in the substrate preparation and the final deprotection steps.[3] The 4-aminobutan-1-ol derivative **5** was obtained from butane-1,4-diol in three steps involving TBS monoprotection, Mitsunobu reaction with SesNHBoc, and acid deprotection.

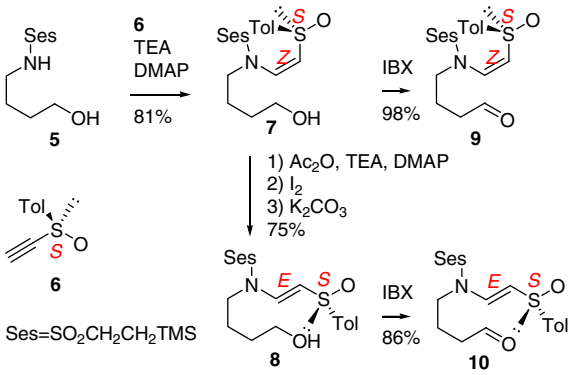
Reaction of **5** with alkynyl sulfoxide **6** in the presence of TEA and DMAP produced a mixture of the (*Z*)-(*S*)- and (*E*)-(*S*)-β-aminovinyl sulfoxides **7** (81%) and **8** (16%). The (*E*)-(*S*)-isomer **8** was also obtained from **7** via acetylation, treatment with iodine, and basic hydrolysis. IBX oxidation[4] of **7** and **8** yielded the corresponding aldehydes **9** and **10**, respectively (Scheme 2).

In the presence of SmI_2 and methanol in THF, the (*Z*)-(*S*)-aldehyde **9** was converted smoothly into the 3-hydroxypiperidine product **11**. No other stereoisomers were detected. The reaction of the (*E*)-(*S*)-isomer **10** proceeded more quickly producing another 3-hydroxypiperidine product **12** (Scheme 3). The structures of the products **11** and **12** were elucidated by X-ray diffraction studies[5] (Fig. 1).

Pummerer rearrangement of the TBS derivatives of the products **11** and **12** and sodium borohydride reduction led to an enantio-



Scheme 1. Stereoselectivity in the SmI_2-mediated cyclization of β-alkoxyvinyl sulfoxides.



Scheme 2. Synthesis of Ses-protected β-aminovinyl sulfoxides.

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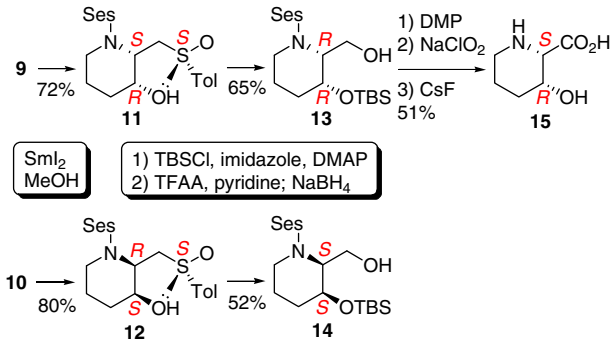


Scheme 3. SmI_2-mediated cyclization of β-aminovinyl sulfoxides.

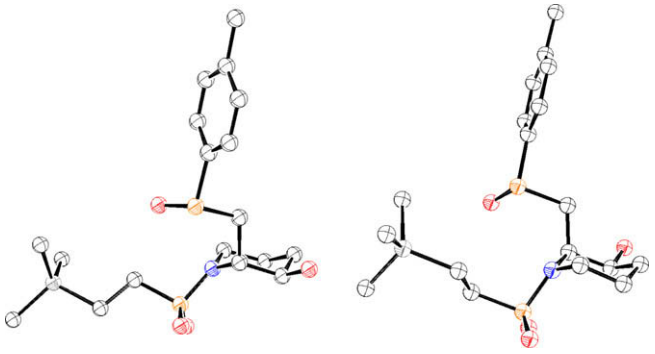
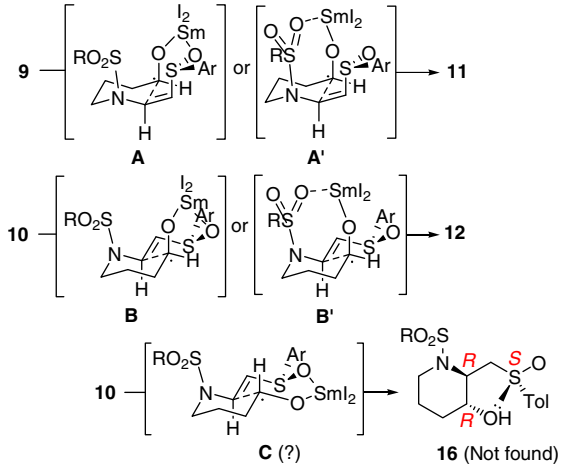


Figure 1. X-ray diffraction structures of **11** and **12**.



Scheme 4. Possible transition state structures in the SmI_2-mediated cyclization of β-aminovinyl sulfoxides.

meric pair of primary alcohols **13** and **14**. Further conversion to (2*S*,3*R*)-3-hydroxypipecolic acid (**15**) involved Dess–Martin oxidation of **13**, Pinnick oxidation and cesium fluoride deprotection. 3-Hydroxypipecolic acids are important building blocks in biologically important compounds.[6]

Formation of the 3-hydroxypiperidine derivative **11** from **9** may be explained by invoking the transition state structure **A**, which is analogous to the transition state structure suggested in the formation of the 3-hydroxyoxane **4**. On the contrary, we were surprised to find that the samarium ketyl from aldehyde **10** cyclized to form the 2,3-*cis* product **12**, presumably through the transition state structure **B**. We had expected formation of the 2,3-*trans* product **16** through the transition state C, but **12** was the sole product. The transition state structures **A**′ and **B**′ may also be considered in which the sulfone oxygens assume active roles in coordination at samarium (Scheme 4).

In these studies, we found that SmI_2-mediated cyclization of aldehydo β-aminovinyl sulfoxides proceeds with high stereoselectivity and unique stereospecificity. Future studies will focus on the synthesis of more complex azacycles using the present concept.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.116.

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2. (a) Kimura, T.; Hagiwara, M.; Nakata, T. *Tetrahedron Lett.* **2007**, *48*, 9171–9175; (b) Nagatomo, M.; Nakata, T. *Heterocycles* **2008**, *76*, 1069–1074.
3. For example, the Cbz-protected derivative did not react with **6**. Ms- and Ts-protection caused problems in the later steps.
4. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
5. CCDC 752450 and 752451 contain the supplementary crystallographic data for **11** and **12**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6. For some recent synthesis of 3-hydroxypipecolic acids, see: (a) Cochi, A.; Burger, B.; Navarro, C.; Pardo, D. G.; Cossy, J.; Zhao, Y.; Cohen, T. *Synlett* **2009**, 2157–2161; (b) Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* **2009**, 2845–2851; (c) Kumar, P. S.; Baskaran, S. *Tetrahedron Lett.* **2009**, *50*, 3489–3492; (d) Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem.* **2008**, *16*, 8273–8286; (e) Liu, L.-X.; Peng, Q.-L.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 1200–1203; (f) Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem.* **2008**, 1789–1796; (g) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3619–3622; (h) Ohara, C.; Takahashi, R.; Miyagawa, T.; Yoshimura, Y.; Kato, A.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1810–1813; (i) Pham, V.-T.; Joo, J.-E.; Tian, Y.-S.; Chung, Y.-S.; Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron: Asymmetry* **2008**, *19*, 318–321; (j) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622–2633; (k) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289–7293; (l) Liang, N.; Datta, A. *J. Org. Chem.* **2005**, *70*, 10182–10185; (m) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360–363; (n) Bodas, M. S.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 8461–8463; (o) Haddad, M.; Larchevêque, M. *Tetrahedron Lett.* **2001**, *42*, 5223–5225.